A CONVENIENT DIFFERENTIAL PROTECTION STRATEGY FOR FUNCTIONAL GROUPS OF SERINE. APPLICATION TO Boc-Ser(Bzl)-OH SYNTHESIS*

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Synthesis of Boc-Ser(Bzl)-OH has been carried out in high yield using a novel differential protection scheme.

The differential protection for serine (Ser) having hydroxyl function in its side chain requires difficult and tedious manipulations. This could be overcome by use of protecting groups cleaved by more than one reagent. In this respect 4-nitrobenzyl (Nbn) group often used for carboxyl protection may be of interest as it was recently reported[1] to be also cleaved by tetrabutylammonium fluoride beside being susceptible to reductive cleavage.

The utility of this differentially protected derivative has been demonstrated by the efficient synthesis of Boc-Ser(Bzl)-OH, the most commonly used derivative in the solid phase peptide synthesis. Methods reported earlier[2 – 4] for the synthesis of Boc-Ser(Bzl)-OH were found to be cumbersome and low yielding (45 – 57%) owing to the limited choice in the availability of protecting groups both from the point of view of selectivity and stability.

In the first step N-protected serine *I* was esterified with 4-nitrobenzyl bromide in the presence of potassium hydrogen carbonate using the procedure of Hamada et al.[5]. As shown in Scheme 1, 4-nitrobenzyl ester *II* was then converted to differentially protected derivative *III* by treatment with silver oxide and benzyl bromide. When the same procedure was applied to the preparation of Boc-Thr(Bzl)-ONbn derivative, a highly impure product was obtained.

Selective removal of Nbn ester can be carried out under very mild and nearly neutral conditions using tetrabutylammonium fluoride in tetrahydrofuran at room temperature

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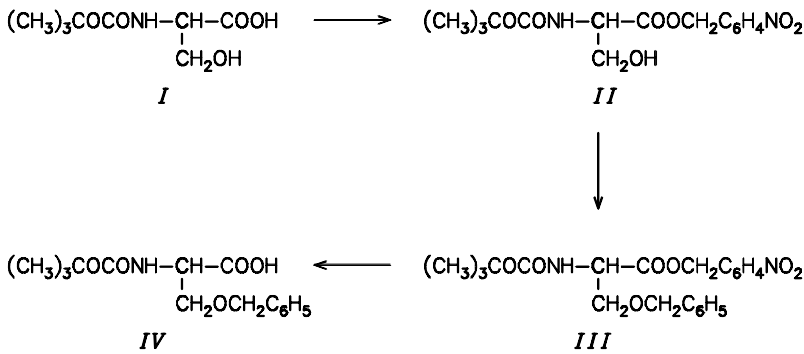

SCHEME 1

in quantitative yield. Deprotection was complete within 5 min and proceeded without any side reaction. Purity of Boc-Ser(Bzl)-OH (*IV*) was established by converting into its cyclohexylamine salt[3,4] and comparing with authentic sample using optical rotation and ^{1}H NMR. The method described hereing is suitable for large scale preparation because of its high efficiency, procedural simplicity and mildness of reaction conditions.

EXPERIMENTAL

Boc-Ser-ONBn (II) (ref.[6]) was synthesized by the procedure reported earlier by Hamada et al.[2] in 92% yield. TLC (ethyl acetate–hexane 1 : 2), R_F 0.62. FAB MS: 363 (M + Na), 341 (M + H). ^{1}H NMR spectrum ($CDCl_3$): 8.1 d, 2 H (ArH); 7.4 d, 2 H (ArH); 5.45 d, 1 H, J = 8.0 (NH); 5.25, 2 H (CH_2Ar); 4.35 m, 1 H (α-CH); 3.9 d, 2 H, J = 3.4 (β-CH_2); 1.34 s, 9 H [$(CH_3)_3C$].

Synthesis of Boc-Ser(Bzl)-ONbn (*III*)

4-Nitrobenzyl derivative *II* (0.68 g, 2 mmol) was added to a mixture of Ag_2O (1.39 g, 6 mmol) and benzyl bromide (0.38 g, 2.2 mmol) in dry DMF. The mixture was stirred at room temperature for 10 h. The solid was filtered off and rinsed with DMF. After the removal of DMF, the residue was purified by chromatography on a column of silica gel using 2% MeOH in $CHCl_3$ as eluant. Chromatographically pure *III* was obtained in 89% yield. TLC (ethyl acetate–hexane 1 : 2), R_F 0.79. $[\alpha]_D^{25}$ −17.5° (*c* 0.8, methanol). FAB MS: 431 (M + H). ^{1}H NMR spectrum ($CDCl_3$): 8.05 d, 2 H (ArH); 7.4 d, 2 H (ArH); 7.18 s, 5 H (ArH); 5.35 d, 1 H, J = 7.8 (NH); 5.16 s, 2 H (CH_2Ar); 5.12 s, 2 H (CH_2Ar); 4.32 m, 1 H (α-CH_2); 3.8 d, 2 H, J = 3.5 (β-CH_2); 1.37 s, 9 H [$(CH_3)_3Cl$]. For $C_{22}H_{26}N_2O_7$ (430.4) calculated: 61.38% C, 6.09% H, 6.51% N; found: 61.7% C, 6.21% H, 6.8% N.

Synthesis of Boc-Ser(Bzl)-OH (*IV*)

A solution of *III* in THF was treated with 1 M tetrabutylammonium fluoride trihydrate (2.4 equivalents) at room temperature. After completion of the reaction (TLC) cold water was added and the solution concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with 5% $KHSO_4$ and with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness.

The residue was treated with cyclohexylamine to get pure cyclohexylamine salt of Boc-Ser(Bzl)-OH, m.p. 158 – 160 °C.

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